



Transcriptomic insights into human brain evolution: acceleration, neutrality, heterochrony

Mehmet Somel¹, Rori Rohlf² and Xiling Liu³

Primate brain transcriptome comparisons within the last 12 years have yielded interesting but contradictory observations on how the transcriptome evolves, and its adaptive role in human cognitive evolution. Since the human-chimpanzee common ancestor, the human prefrontal cortex transcriptome seems to have evolved more than that of the chimpanzee. But at the same time, most expression differences among species, especially those observed in adults, appear as consequences of neutral evolution at *cis*-regulatory sites. Adaptive expression changes in the human brain may be rare events involving timing shifts, or heterochrony, in specific neurodevelopmental processes. Disentangling adaptive and neutral expression changes, and associating these with human-specific features of the brain require improved methods, comparisons across more species, and further work on comparative development.

Addresses

¹ Department of Biology, Middle East Technical University, Ankara, Turkey

² Department of Integrative Biology, University of California, Berkeley, CA, USA

³ Key Laboratory of Computational Biology, CAS-MPG Partner Institute for Computational Biology, Shanghai Institutes for Biological Sciences, Shanghai, China

Corresponding author: Somel, Mehmet (somel.mehmet@gmail.com, somel.mehmet@googlemail.com)

Current Opinion in Genetics & Development 2014, 29:110–119

This review comes from a themed issue on **Genetics of human origin**

Edited by **Aida Andes** and **Katja Nowick**

<http://dx.doi.org/10.1016/j.gde.2014.09.001>

0959-437X/© 2014 Elsevier Ltd. All rights reserved.

Introduction

Humans are efficient cultural accumulators and niche constructors [1,2]. However, this is not because they are individually superior over other animals in every cognitive aspect. Chimpanzee performance in physical intelligence tests [3] or working memory tasks [4,5] appears comparable to infant or adult humans. The difference rather lies in human social intelligence and abilities, including spoken language, prosocial and cooperative behavior, and inclination to learn and teach [1,6]. These characters, in turn, are associated with

human-specific changes in brain development, anatomy, and physiology.

Comparative anatomical studies indicate that human and chimpanzee brain structure and developmental patterns closely resemble one another, relative to other primates (reviewed in [7–9]). Thus, most major characteristics of the human brain evolved in the great ape common ancestor. But species differences do exist, including three times more neurons and lower neuron density in the cortex, increased dendritic arbor, new connections, and prolonged development of the human brain relative to the chimpanzee brain (Table 1). The aim is, on the one hand, to predict the cognitive and behavioral consequences of these structural novelties; on the other, to identify the underlying human-specific genetic changes. The latter will inform on how human evolution unfolded, for example, whether it involved numerous genetic changes of small effect, or few with large effect. It can also allow partial reconstruction of human evolutionary history by comparison with extinct hominins with known genomes, such as Neanderthals and Denisovans (e.g. [10,11,12]).

Evolutionary changes in brain structure, developmental timing, or neuronal physiology can arise from two types of effects. The first type is rather qualitative; it involves changes in protein activity through emergence of new genes, protein domains, or single amino acid changes. Between human and chimpanzee, coding differences are common (about two amino acids per ortholog), but most of these substitutions are predicted to be neutral [13]. Also, there exist very few human *de novo* genes [14,15]. The second type is relatively quantitative and involves expression changes, that is, changes in mRNA and protein abundance. These occur through *cis* effects (copy number, enhancer, promoter, UTR sequence changes) or *trans* effects (changes in transcription factor [TF], microRNA, DNA methyltransferase and chromatin modifier activity or post-translational modifications) [16].

Comparative developmental studies in animal models clearly demonstrate the role of gene expression changes, in the level, timing, location, or splicing pattern, as major contributors to the evolution of new forms and adaptive functions [17,18]. Developmental expression changes are frequently driven by small alterations in *trans* effectors' coding or regulatory sequence, modifying gene expression networks and reorganizing existing modular processes (e.g. extension of progenitor mitotic activity).

Table 1

Anatomical, histological and molecular features of the human brain relative to those of chimpanzees.**A – Anatomy and connections**

- a. ~3 times larger volume; ~3 times more neurons; higher encephalization [105].
- b. Higher proportion of neocortex, especially the prefrontal and temporal cortices; increased cerebellar connections; increased connections within the prefrontal cortex [8,105].
- c. Slightly higher cortical folding (gyrification) in the neocortex, especially in the PFC [106].
- d. Larger temporal cortex white matter [107].
- e. Relative enlargement and increased left-right asymmetry in the Broca's area [108].
- f. Expanded white-matter connection between frontal and temporal cortices, which could be related to language use [109].
- g. Possible loss of a network hub in the medial PFC [110].

B – Cell types and histology

- a. Higher glia to neuron ratio [38**].
- b. Higher proportion of large spindle projection neurons in layer V (but little difference in pyramidal or fusiform cells) [111].
- c. Wider interneuronal spacing, or neuropil, in the PFC than in other cortical regions, indicating higher dendrite, spine, axon density [112,113] (a feature which develops after adolescence [114]).
- d. Wider interneuronal spacing in the Broca's area [115].
- e. Wider minicolumns and more interneuronal spacing on the left hemisphere [116].
- f. Assymetry in interneuronal spacing in the left hemisphere [116].
- g. Longer dendrites in cortical neurons [117].
- h. Higher total number but lower density of von Economo neurons (spindle cells) [118].

C – Development and aging

- a. Faster brain growth starting from 16 weeks of gestation [119] and continuing into infancy [120].
- b. Faster PFC white matter volume growth during postnatal development [121].
- c. Extended duration of cortical myelination [36].
- d. Delayed peak of synapse numbers in PFC [64**] (but see [95]).
- e. Relatively earlier initiation of white matter decay [122].
- f. Prominent brain shrinkage at old age [123].

D – Physiology

- a. Higher levels of resting-state brain activity in language areas [124].
- b. Higher activity of metabolic pathways [22,30*,125,126].

Intuitively, developmental expression changes might have played similar roles in human brain evolution [19**]. Hence, once microarray technology became available, multiple groups moved to compare mRNA abundance between human and chimpanzee adult cortical regions and other tissues. The expectation was that a few genes would exhibit prominent activation shifts on the human lineage, and these could be readily associated with human-specific traits. On the contrary, the first studies found that hundreds to thousands of genes showed significant mRNA abundance differences between humans and chimpanzees [20,21**,22], most with ambiguous functional roles. Furthermore, many of these species differences were shared across brain regions with distinct functions [23] (reviewed in [24]).

Human acceleration?

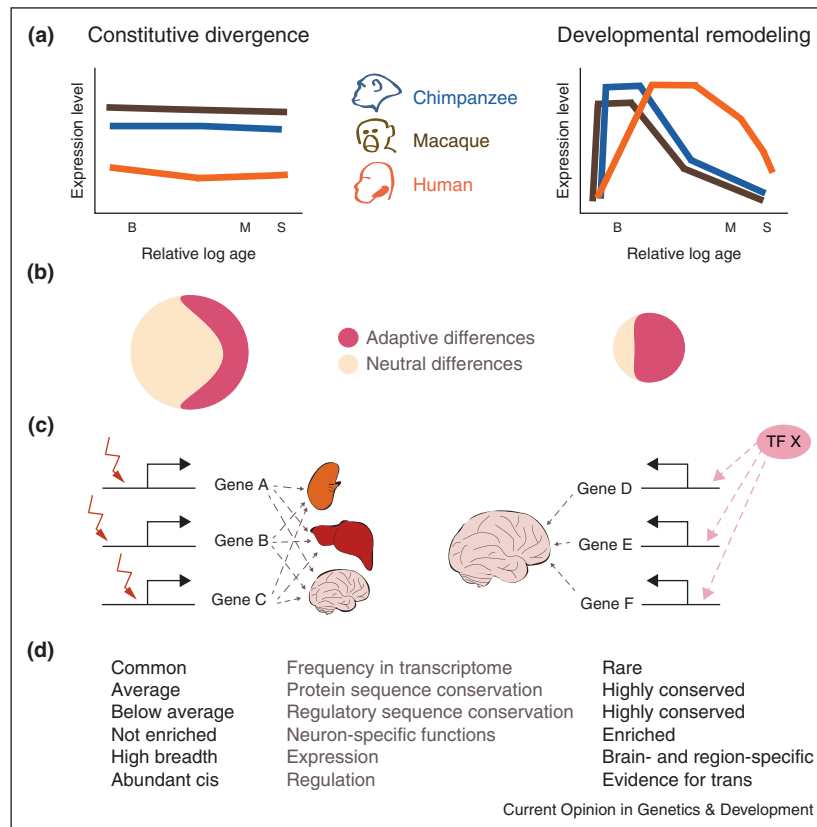
Despite this initial disappointment, some of the early studies found an excess of gene expression change on the human lineage, or human acceleration. One study detected five times more human-specific expression changes than chimpanzee-specific ones, and only in the brain, but not blood or liver [21**]. Another found dozens of genes with elevated expression only in humans, including genes with roles in synaptic plasticity (e.g. calcium/calmodulin-dependent protein kinase II alpha, *CAMK2A*, and carbonic anhydrase II, *CA2*) [20].

Human brain acceleration is intriguing, as the brain transcriptome is highly conserved compared to most other tissues, and brain-specific genes' coding sequences are under strong negative selection [25,26*]. Also notably, these studies had investigated expression levels in the prefrontal cortex (PFC), a region involved in high order, partly human-specific cognitive processes such as abstract thinking and planning [27]. An abundance of human-specific molecular changes in a highly conserved tissue with human-specific functions was suggestive of adaptive evolution. It supported the old notion that the human brain transcriptome divergence could explain human cognitive divergence [19**].

Subsequent work, however, revealed equivocal results. Some, using different brain regions [22] or technology [28], reported similar magnitude of change on the human and chimpanzee lineages. Another found higher similarity between human and gorilla brain transcriptomes than with the chimpanzee, implying chimpanzee acceleration (although the effect here was not quantified) [26*].

Yet others reported human acceleration but in specific contexts. An investigation into metabolome and metabolite-related enzymes did find more adult human-specific changes in the PFC than chimpanzee-specific changes

Figure 1



Two types of transcriptome divergence, constitutive divergence (CD) and developmental remodeling (DR), are described in schematic diagrams, on the left and right panels, respectively. **(a)** Hypothetical examples of CD and DR as observed in comparative expression levels over age (B: birth, M: maturity, S: senescence; maturity is closer to senescence using log-transformed age models); **(b)** rough relative frequencies of CD and DR including the approximate hypothesized proportions of neutral versus adaptive differences in each; **(c)** the regulatory properties of CD and DR: *cis* and *trans* mechanisms predicted to be dominating each, and having high and low expression breadth, respectively; **(d)** a table contrasting their observed characteristics, in the categories listed in the middle column. Although CR is the predominant divergence type observed in the transcriptome, we suggest that DR might have played the main role in human cognitive evolution. Both hypotheses and data based on [34**].

[29]. But surprisingly, the skeletal muscle metabolome showed human acceleration even stronger than the PFC [30*]. Using comparative gene expression network analysis of correlated expression patterns between human, chimpanzee and macaque brains [31,32], one study identified more human-specific than chimpanzee-specific co-expression modules in the frontal pole, but not in caudate nucleus [33*]. Another study sorted human, chimpanzee and macaque brain expression differences into those involving developmental pattern differences (developmental remodeling), and those constitutive across postnatal development (i.e. same gene expression difference found both in newborns and in adults) (Figure 1) [34**]. Humans and chimpanzees showed similar levels of constitutive divergence, but humans showed higher intensity of developmental remodeling (see below).

One possibility is that human acceleration in the brain is caused by technical issues: difficulties in obtaining

homologous brain structures, environmental differences, or microarray hybridization or RNA-sequencing read alignment artifacts could all create human-specific biases. In multiple studies reporting human transcriptome acceleration in PFC, other brain regions (e.g. visual cortex, caudate nucleus, cerebellum) exhibited little or no acceleration [30*,33*,34**], arguing against purely technical biases. Still, more heterogeneous tissue composition or expression of more recently duplicated genes in the PFC could create region-specific effects. This awaits future investigation.

The acceleration signal is clearly more pronounced in the PFC than other brain regions. Not only did the human PFC acquire new cognitive functions, but it also underwent dramatic enlargement and changes in developmental timing [35,36] (Table 1). In fact, structural expansion and developmental timing changes themselves generate shifts in tissue composition, which translate into differences in cell type proportions within the

tissue. Expression changes may then reflect differences in cell type ratios, as shown in blood [37]. Indeed, glia/neuron ratio in the human adult PFC appears significantly higher than in chimpanzees [38**] and glia-specific energy metabolism genes (e.g. *CA2*) appear up-regulated in human [20]. Acceleration of the adult human brain transcriptome may thus be largely a consequence of earlier developmental shifts and tissue composition changes, rather than cell-autonomous changes.

Neutral divergence?

Human and non-human primate comparisons yielded another set of stimulating observations, that (a) genes showing high mRNA level divergence between species also show high diversity within species (which are probably genes under weaker negative selection); (b) gene expression differences tend to accumulate linearly over evolutionary time [22,39**], revealing a phylogenetic signal similar to accumulating neutral mutations [40] (but might taper off in the long run [26*,41*]); (c) genes showing the highest expression divergence also evolve at faster, relaxed rates in their coding sequence [25]; (d) the major type of brain transcriptome divergence, constitutive divergence, involves broadly expressed genes without brain-specific functions and with below-average sequence conservation; and these appear driven by *cis* effects [34**] (Figure 1).

These observations raise the possibility that transcriptome evolution is largely shaped by a combination of negative selection and neutral genetic drift. The bulk of detected expression divergence is caused by accumulating neutral *cis* mutations [39**,42], instead of positive selection. The idea of neutral transcriptome evolution was initially contested [43,44] but today it seems better recognized (e.g. [45]). Still, alternative models do exist (see below).

Neutral *cis*-driven divergence may affect other aspects of gene regulation. Cerebellar splicing differences between humans and other primates appeared largely *cis*-driven and showed limited tissue-specificity [46]; tissue-specificity in splicing was particularly lower than observed using mRNA levels [47]. Another study on A-to-I RNA editing differences between humans and other primates in PFC and cerebellum, found more RNA editing differences between species than between brain regions or developmental stages [48]. This implies rapid evolution, and possibly, relaxed constraints. Also interestingly, genes linked to hundreds of human PFC-specific H3K4me3 gains, a marker of open chromatin, showed no specific association with neuronal activity; nearly 1/4 of these genes had DNA methylation signatures in the direction of higher gene activity in sperm [49]. Thus, not just constitutive mRNA level differences, but also a significant portion of splicing, RNA editing and histone

modification differences between humans and other species' brains appear to be ubiquitously expressed, not brain-specific. Fast evolution and broad expression breadth imply that many differences are driven by neutral *cis* mutations and represent phenotypically silent molecular changes.

Phenotypic silence can also arise from expression differences canceling each other out or being buffered. In adult primate brain transcriptome data, numerous small down-regulations, perhaps representing slightly deleterious *cis* fixations, could be compensated by rare large up-regulations, which could be adaptive [50,51]. Meanwhile, many mRNA level species differences may not be translated, as shown in human and chimpanzee cell lines [52*].

Functional and adaptive divergence?

How to then identify mRNA abundance changes with phenotypic effect and adaptive roles in human cognitive evolution? In comparisons involving few species, the classical ANOVA approach will be insufficient to rule out neutrality (Box 1). Additional information is required. If multiple functionally-related genes show expression change in the same direction (e.g. up-regulation), this is an indication of a pathway being altered, with likely phenotypic consequence. Such co-divergence could be caused by a single *trans* change (e.g. up-regulation of a shared TF), itself driven by environmental differences between species, adaptive evolution, or genetic drift. Co-divergence could also be caused by multiple *cis* changes in the *same* direction, implying positive selection (as demonstrated in yeast [53,54]). In primates, however, linking expression divergence to causal *cis* changes has difficulties.

One alternative approach for identifying putative functional expression differences involves searching for lineage-specific expression shifts in highly conserved processes. For this, one can compare human expression levels to numerous diverse species (e.g. [55]) (Box 1). One can also compare humans' and other primates' transcriptomes during development, when even small changes produce large phenotypic outcomes [9,17*,56]. As argued above, functional gene expression changes observed in adults either reflect cell-autonomous changes in physiology (e.g. higher aerobic metabolism) or shifts in cell type composition or cellular anatomy (e.g. higher glia ratios or longer dendrites). As the latter is driven by modular changes in conserved developmental pathways, it makes double sense to study ontogenesis.

A role for heterochrony

The few studies on comparative primate postnatal brain development transcriptomics published to date, made interesting points. In the PFC and cerebellum, 50–70% of the expressed genes show changes in mRNA abundance during postnatal development and aging, with the

Box 1 Models for identifying differential expression

A major goal in comparative expression studies is to identify genes with differing expression between species, which may be caused by adaptive evolution. Earlier microarray-based comparative expression analyses generally relied on ANOVA-style analyses to detect genes with high expression variance between species, as compared to within species [42,43,78–82] (reviewed in [83]). The ANOVA approach effectively identifies genes with different mean expression levels between species, given the degree of expression variance within species.

However, applying ANOVA assumes independence between species, implicitly ignoring different divergence times. As more species are included in a study, it becomes important to consider differences in expression between species in the context of their varying phylogenetic relationships [84]. For example, using ANOVA, a neutral expression shift on a long phylogenetic branch may be misinterpreted as an adaptive shift, while a relatively small, but biologically meaningful expression shift on a short branch may be overlooked.

A number of researchers have considered phylogenetic correlations by modeling expression evolution as an Ornstein-Uhlenbeck (OU) process [41*,85–87]. An OU process can be thought of as a random walk with some pull towards a particular value. In the expression evolution analogy, an OU process models expression level drift over evolutionary time with some stabilizing selection towards an optimal value, as is common in quantitative comparative studies [88]. If that stabilizing selection is reduced to zero, the OU process models pure drift. Adaptive shifts in expression can be modeled using branch-specific optimal expression levels. Using these different evolutionary regimes, specific tests can be performed querying expression level shifts, stabilizing selection, and drift (but see [89]). With these advantages, OU processes are emerging as a convenient and relevant framework for investigation of adaptive expression hypotheses [26*,41*,55,89,90,91].

OU models have been applied to comparative time series expression data, treating each time point independently, to elucidate the evolution of development [90]. Further sophistication of these methods is required for a unified expression model over evolutionary and developmental time. Additionally, variance within species must be considered in phylogenetic methods [89,91]. As these studies illuminate mechanisms of expression level evolution (for example, mutational effect on expression level [92]), models must be flexible enough to incorporate this changing information.

most rapid changes taking place in newborns [34**,57,58]. 30–50% of these genes, as well as genes not showing developmental regulation in the brain, display constitutive expression divergence (Figure 1) [34**]. Meanwhile, developmental trajectories (i.e. the timing of mRNA abundance changes) are generally conserved: if a human gene is up-regulated during postnatal development, >80% of the time, its macaque ortholog is also up-regulated [58]. Trajectories are still, but less conserved during aging [58] (in contrast to [59]).

Developmental trajectory differences, or remodeling, are rare and appear as shifts in timing, instead of novel trajectories. Most timing differences scale with life-history differences, reflecting human altriciality and ~1.5 times slower maturation relative to chimpanzees [60,61]. Interestingly, timing shifts are not uniform across genes: some genes' expression profiles reveal

heterochrony (greater delay or acceleration relative to maturation rate difference between species [62,63**]), with bias towards human delays [57].

Heterochronic expression differences themselves have a number of characteristics [34**]: (a) they occur as coordinated changes across hundreds of neural function-associated genes; (b) in the PFC, they happen 5 times more in the human lineage than the chimpanzee lineage, but less so in the cerebellum; (c) they are brain region-specific; (d) intriguingly, genes showing the strongest remodeling effects are the most conserved in their protein and regulatory sequences, arguing against major *cis* contribution to remodeling; (e) TF and microRNA show more human-specific remodeling than their putative targets. Also, several of these human-specific microRNA expression patterns were linked to expression changes in their targets *in vitro*, providing an explanation for co-divergence across hundreds of genes [34**].

A follow-up study on these expression profiles found evidence for an exceptionally delayed/extended period of high synaptic density in the human PFC [64**] (Box 2). This heterochronic phenotype, driven by *trans* regulators, could enhance learning and cultural transmission in humans [1,61].

Extended synaptogenesis is yet the only transcriptomic example of human heterochrony possibly linked to phenotypic differences. Meanwhile, many other evolutionary changes in the human brain could involve similar heterochronic, *trans*-regulated changes in core neurodevelopmental modules: for example, shifts in the duration and rate of symmetric and asymmetric progenitor divisions, enhanced signaling for dendritic arborization and gliogenesis, or prolonged myelination (Table 1). Comparative genomic studies have already identified candidate human-specific genetic changes causing heterochrony: for example, loss of a conserved enhancer, which could increase neuron numbers by restricting a mitotic inhibitor (growth arrest and DNA-damage-inducible gamma, *GADD45G*) deployed in brain development [65]; or gain of a truncated SLIT-ROBO rho GTPase activating protein 2 (*SRGAP2*) copy, which could promote spine density in the human neocortex by restricting *SRGAP2A*, a limiting agent in spine development [66*].

Neurodevelopmental genes, TFs and microRNAs interestingly pop up in various genome scans for human-specific changes, either in non-coding intergenic RNA [65,67,68], in recent segmental duplications [69], among recently evolved primate [70] or human [14,71] genes, among genes with divergent promoters in humans [72], or modern human-specific substitutions not shared with Neanderthals [10]. This implies liberal introduction of novel regulatory and coding sequence variants into neurodevelopmental networks and major remodeling of

Box 2 Heterochrony and extended synaptogenesis in humans

A recent study on postnatal brain development in humans, chimpanzees and macaques demonstrated how transcriptome analyses can inform about phenotypic divergence [64**]. In this dataset, genes involved in synaptogenesis and synaptic elimination in the PFC showed significantly delayed changes in humans. Neither synaptic expression in cerebellum, nor other processes such as myelination or axonogenesis in PFC, showed comparable delay (but see [36]). Metabolomic, proteomic and electron microscopy data from the same samples similarly indicated a difference in synaptic density between human newborns and other species [64**].

In fact, delayed synaptic maturation in human PFC relative to macaque had been known, but whether this was human-specific, or hominoid-specific, had remained unclear [93]. According to this study, peak density of synapses in PFC (later removed by synaptic pruning [94]) occurs shortly after birth in macaque and chimpanzee, but in humans, at around 3–5 years of age [64**] (but see [95]). The delayed peak can also be observed in peak aerobic glycolysis around the same period [96].

It was long suggested that a simple shift in life-history extending the infantile period could have aided rapid cultural accumulation across human generations, by allowing more time for learning [1,61,62,97]. The transcriptomic results imply that the early period of high synaptic plasticity, when learning is most rapid [93] (reviewed in [98–100]), was particularly extended. Human heterochrony is therefore not ubiquitous, but alters synaptic maturation in a specific brain region. Although enhancing learning in children, such heterochrony may also translate into synaptic activity and metabolism differences between adult humans and chimpanzees as observed earlier [20].

Bioinformatic analysis implicated myocyte enhancer factor 2A (*MEF2A*), a TF with roles in synaptic maturation and elimination, as the central regulator of human-specific delay in synaptic gene expression. Delayed expression of *MEF2A* in human PFC could then drive delayed synaptic maturation. Differential phosphorylation and sumoylation of *MEF2A* [101] between human and chimpanzee development could also contribute to downstream transcriptomic differences.

How is *MEF2A* mRNA abundance itself differentially regulated? As *MEF2A* regulation is activity-dependent [101,102], social/environmental differences between species could be responsible. Other possibilities include (perhaps prenatal) *trans* effects influencing *MEF2A*, or *cis* effects in *MEF2A*'s own regulatory sequence. An interesting finding here was a putative signature of recent positive selection upstream of *MEF2A*, dating after the split with Neanderthals [64**]. Although tentative, this result implies that delayed *MEF2A* signaling may be *cis* driven and that delayed synaptogenesis arose late in human evolution [103]. If delayed synaptic maturation also extended the vulnerable phase in human infancy, such delay might have only recently been possible, after sufficient technological advance [104].

human brain development. It thus contradicts the notion of conserved postnatal brain development among primates. This could have three explanations: (a) human-specific sequence changes mainly modify prenatal development [70], not yet directly compared between humans and chimpanzees; (b) remodeling involves numerous *cis* changes that fine-tune *trans* changes of large effect, and fine tunings are not detectable using current technology; (c) constraints on human brain development are relaxed. Distinguishing among these possibilities is a forthcoming challenge.

Future prospects

Transcriptome comparisons hitherto provided insight into general evolutionary processes and specific adaptive mechanisms shaping human brain evolution. One is the apparent predominance of negative selection and neutral changes in shaping adult species differences in mRNA abundance. Another is the role of heterochrony shaping specific processes (Box 2). Still, these are yet preliminary steps in understanding the genetic basis of human-specific cognitive phenotypes.

One way forward is studying under-investigated brain regions like the hippocampus or temporal cortex. Given that many adult expression differences simply reflect cell type composition differences, another approach could be cell type-specific [73] or single cell profiling. But the most promising endeavor might be focusing on comparative development and extending into the prenatal period. Although access to fetal tissue poses an obstacle, this can be partly overcome through comparative testing of human-specific *cis* changes for heterochronic action in mouse models (e.g. [74,75]), or studying human and chimpanzee development at the transcriptome level using organoids [9].

Finally, developmental mechanisms of human-specific phenotypic changes, such as delayed brain development, could also be in play in distant taxa. For instance, it was suggested that dogs have neotenus characters compared to wolves [76], while social insects may have neotenus brains compared to other insects [77]. Meta-analyses of brain development mechanisms across diverse social taxa could be another worthwhile strategy in understanding human evolution.

Acknowledgements

M.S. was supported by the Scientific And Technological Research Council Of Turkey (Program 2232, grant no: 114C040) and a BAGEP Award from The Science Academy, Turkey (Bilim Akademisi). R.R. was supported by the United States National Science Foundation award 1103767. X.L. was supported by the Science and Technology Commission of Shanghai Municipality (grant no: 13ZR1464200) and the Knowledge Innovation Program of Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences (grant no: 2013KIP215).

References and recommended reading

- of special interest
 - of outstanding interest
1. Hill K, Barton M, Hurtado AM: **The emergence of human uniqueness: characters underlying behavioral modernity.** *Evol Anthropol* 2009, **18**:187-200.
 2. Laland KN, Odling-Smee J, Myles S: **How culture shaped the human genome: bringing genetics and the human sciences together.** *Nat Rev Genet* 2010, **11**:137-148.
 3. Herrmann E, Call J, Hernández-Lloreda MV, Hare B, Tomasello M: **Humans have evolved specialized skills of social cognition: the cultural intelligence hypothesis.** *Science* 2007, **317**:1360-1366.

4. Inoue S, Matsuzawa T: **Working memory of numerals in chimpanzees**. *Curr Biol* 2007, **17**:R1004-R1005.
5. Cook P, Wilson M: **Do young chimpanzees have extraordinary working memory?** *Psychon Bull Rev* 2010, **17**:599-600.
6. Tennie C, Call J, Tomasello M: **Ratcheting up the ratchet: on the evolution of cumulative culture**. *Philos Trans R Soc Lond B Biol Sci* 2009, **364**:2405-2415.
- A study comparing learning processes between humans and chimpanzees, concluding that social learning in humans has fundamentally different qualities than in chimpanzees.
7. Sherwood CC, Bauernfeind AL, Bianchi S, Raghanti MA, Hof PR: **Human brain evolution writ large and small**. *Prog Brain Res* 2012, **195**:237-254.
8. Rilling JK: **Human and nonhuman primate brains: are they allometrically scaled versions of the same design?** *Evol Anthropol* 2006, **15**:65-77.
9. Geschwind DH, Rakic P: **Cortical evolution: judge the brain by its cover**. *Neuron* 2013, **80**:633-647.
10. Prufer K, Racimo F, Patterson N, Jay F, Sankararaman S, Sawyer S, Heinze A, Renaud G, Sudmant P, de Filippo C *et al.*: **The complete genome sequence of a Neanderthal from the Altai mountains**. *Nature* 2013, **505**:43-49.
- Report of the first high quality Neanderthal genome. By comparing Neanderthal and Denisovan genomic data with those of humans, the authors draw a list of mutations that fixed in the modern human lineage, including numerous mutations in neurodevelopmental genes.
11. Green RE, Krause J, Briggs AW, Maricic T, Stenzel U, Kircher M, Patterson N, Li H, Zhai W, Fritz MH-Y *et al.*: **A draft sequence of the Neanderthal genome**. *Science* 2010, **328**:710-722.
12. Reich D, Green RE, Kircher M, Krause J, Patterson N, Durand EY, Viola B, Briggs AW, Stenzel U, Johnson PLF *et al.*: **Genetic history of an archaic hominin group from Denisova cave in Siberia**. *Nature* 2010, **468**:1053-1060.
13. Mikkelsen T, Hillier L, Eichler E, Zody M, Jaffe D, Yang S-P, Enard W, Hellmann I, Lindblad-Toh K, Altheide T *et al.*: **Initial sequence of the chimpanzee genome and comparison with the human genome**. *Nature* 2005, **437**:69-87.
14. Li C-Y, Zhang Y, Wang Z, Zhang Y, Cao C, Zhang P-W, Lu S-J, Li X-M, Yu Q, Zheng X *et al.*: **A human-specific de novo protein-coding gene associated with human brain functions**. *PLoS Comput Biol* 2010, **6**:e1000734.
15. Knowles DG, McLysaght A: **Recent de novo origin of human protein-coding genes**. *Genome Res* 2009, **19**:1752-1759.
16. Wilson MD, Odom DT: **Evolution of transcriptional control in mammals**. *Curr Opin Genet Dev* 2009, **19**:579-585.
17. Carroll SB: **Evo-devo and an expanding evolutionary synthesis: a genetic theory of morphological evolution**. *Cell* 2008, **134**:25-36.
- An illuminating review that pushes forward the idea that novelty in animal form mainly involves remodeling of gene expression networks.
18. Moss EG: **Heterochronic genes and the nature of developmental time**. *Curr Biol* 2007, **17**:R425-R434.
19. King M, Wilson A: **Evolution at two levels in humans and chimpanzees**. *Science* 1975, **188**:107-116.
- The classical study of comparative human and chimpanzees gene sequences, claiming that protein sequence differences cannot explain human phenotypic divergence, and developmental expression differences must be in play.
20. Cáceres M, Lachuer J, Zapala MA, Redmond JC, Kudo L, Geschwind DH, Lockhart DJ, Preuss TM, Barlow C: **Elevated gene expression levels distinguish human from non-human primate brains**. *Proc Natl Acad Sci U S A* 2003, **100**:13030-13035.
21. Enard W, Khaitovich P, Klose J, Zollner S, Heissig F, Giavalisco P, Nieselt-Struwe K, Muchmore E, Varki A, Ravid R *et al.*: **Intra- and interspecific variation in primate gene expression patterns**. *Science* 2002, **296**:340-343.
- The first microarray comparison of human and chimpanzee transcriptomes that reported acceleration of evolutionary expression changes in the human brain.
22. Uddin M, Wildman D, Liu G, Xu W, Johnson R, Hof P, Kapatos G, Grossman L, Goodman M: **Sister grouping of chimpanzees and humans as revealed by genome-wide phylogenetic analysis of brain gene expression profiles**. *Proc Natl Acad Sci U S A* 2004, **101**:2957-2962.
23. Khaitovich P, Muetzel B, She X, Lachmann M, Hellmann I, Dietzsch J, Steigle S, Do H-H, Weiss G, Enard W *et al.*: **Regional patterns of gene expression in human and chimpanzee brains**. *Genome Res* 2004, **14**:1462-1473.
24. Khaitovich P, Enard W, Lachmann M, Paabo S: **Evolution of primate gene expression**. *Nat Rev Genet* 2006, **7**:693-702.
25. Khaitovich P, Hellmann I, Enard W, Nowick K, Leinweber M, Franz H, Weiss G, Lachmann M, Paabo S: **Parallel patterns of evolution in the genomes and transcriptomes of humans and chimpanzees**. *Science* 2005, **309**:1850-1854.
26. Brawand D, Soumillon M, Necsulea A, Julien P, Csárdi G, Harrigan P, Weier M, Liechti A, Aximu-Petri A, Kircher M *et al.*: **The evolution of gene expression levels in mammalian organs**. *Nature* 2011, **478**:343-348.
- The first comprehensive RNA-sequencing study of mammalian tissues across diverse taxa, which interestingly finds higher similarity between human and gorilla transcriptomes in brain, testis and other tissues, relative to those of chimpanzee.
27. Wood JN: **Social cognition and the prefrontal cortex**. *Behav Cogn Neurosci Rev* 2003, **2**:97-114.
28. Babbitt C, Fedrigo O, Pfefferle A, Boyle A, Horvath J, Furey T, Wray G: **Both noncoding and protein-coding RNAs contribute to gene expression evolution in the primate brain**. *Genome Biol Evol* 2010, **2010**:67.
29. Fu X, Giavalisco P, Liu X, Catchpole G, Fu N, Ning Z-B, Guo S, Yan Z, Somel M, Pääbo S *et al.*: **Rapid metabolic evolution in human prefrontal cortex**. *Proc Natl Acad Sci U S A* 2011, **108**:6181-6186.
30. Bozek K, Wei Y, Yan Z, Liu X, Xiong J, Sugimoto M, Tomita M, Pääbo S, Pieszek R, Sherwood C *et al.*: **Exceptional evolutionary divergence of human muscle and brain metabolomes parallels human cognitive and physical uniqueness**. *PLoS Biol* 2014, **12**:e1001871EP.
- A comparison of metabolomic differences between human, chimpanzee, macaque and mouse across multiple tissues. The authors reported more human-specific changes in muscle, than in PFC, and suggested that muscle metabolome remodeling could be related to increased energy expenditure in the human brain.
31. Nowick K, Gernat T, Almaas E, Stubbs L: **Differences in human and chimpanzee gene expression patterns define an evolving network of transcription factors in brain**. *Proc Natl Acad Sci U S A* 2009, **106**:22358-22363.
32. Oldham M, Horvath S, Geschwind D: **Conservation and evolution of gene coexpression networks in human and chimpanzee brains**. *Proc Natl Acad Sci U S A* 2006:0605938103.
33. Konopka G, Friedrich T, Davis-Turak J, Winden K, Oldham MC, Gao F, Chen L, Wang G-Z, Luo R, Preuss TM *et al.*: **Human-specific transcriptional networks in the brain**. *Neuron* 2012, **75**:601-617.
- A comparison of human and chimpanzee transcriptomes at the level of gene co-expression networks.
34. Somel M, Liu X, Tang L, Yan Z, Hu H, Guo S, Jiang X, Zhang X, Xu G, Xie G *et al.*: **MicroRNA-driven developmental remodeling in the brain distinguishes humans from other primates**. *PLoS Biol* 2011, **9**:e1001214.
- This study classified expression differences into constitutive and developmental remodeling types, and claimed that human-specific, adaptive changes mainly involve the latter.
35. Rilling JK, Insel TR: **Differential expansion of neural projection systems in primate brain evolution**. *Neuroreport* 1999, **10**:1453-1460.
36. Miller DJ, Duka T, Stimpson CD, Schapiro SJ, Baze WB, McArthur MJ, Fobbs AJ, Sousa AMM, Sestan N, Wildman DE *et al.*: **Prolonged myelination in human neocortical evolution**. *Proc Natl Acad Sci U S A* 2012, **109**:16480-16485.

37. Tung J, Barreiro LB, Johnson ZP, Hansen KD, Michopoulos V, Toufexis D, Michelini K, Wilson ME, Gilad Y: **Social environment is associated with gene regulatory variation in the rhesus macaque immune system.** *Proc Natl Acad Sci U S A* 2012, **109**:6490-6495.
38. Sherwood C, Stimpson C, Raghanti M, Wildman D, Uddin M, Grossman L, Goodman M, Redmond J, Bonar C, Erwin J *et al.*: **Evolution of increased glia-neuron ratios in the human frontal cortex.** *Proc Natl Acad Sci U S A* 2006. 0605843103.
- This study finds higher glia-to-neuron ratios in the human PFC, although the ratio itself scales with brain size. High glia density could be associated with higher metabolic costs of human neurons with long dendrites and axons.
39. Khaitovich P, Weiss G, Lachmann M, Hellmann I, Enard W, Muetzel B, Wirkner U, Ansorge W, Pääbo S: **A neutral model of transcriptome evolution.** *PLoS Biol* 2004, **2**:E132.
- This study put forward the notion of neutral transcriptome evolution using primate microarray data available at the time, suggesting that transcriptome divergence in protein coding genes can be even comparable to pseudogenes. Although initially contested, the main points of this paper appear valid today.
40. Kimura M: **Evolutionary rate at the molecular level.** *Nature* 1968, **217**:624-626.
41. Bedford T, Hartl DL: **Optimization of gene expression by natural selection.** *Proc Natl Acad Sci U S A* 2009, **106**:1133-1138.
- An application of the Ornstein-Uhlenbeck model to *Drosophila* transcriptome data, reporting widespread stabilizing selection on gene expression.
42. Oleksiak M, Churchill G, Crawford D: **Variation in gene expression within and among natural populations.** *Nat Genet* 2002, **32**:261.
43. Gilad Y, Oshlack A, Smyth GK, Speed TP, White KP: **Expression profiling in primates reveals a rapid evolution of human transcription factors.** *Nature* 2006, **440**:242-245.
44. Lynch M: *The Origins of Genome Architecture*. Sinauer Associates; 2007.
45. Albert FW, Somel M, Carneiro M, Aximu-Petri A, Halbwax M, Thalmann O, Blanco-Aguir JA, Plyusnina IZ, Trut L, Villafuerte R *et al.*: **A comparison of brain gene expression levels in domesticated and wild animals.** *PLoS Genet* 2012, **8**:e1002962.
46. Lin L, Shen S, Jiang P, Sato S, Davidson BL, Xing Y: **Evolution of alternative splicing in primate brain transcriptomes.** *Hum Mol Genet* 2010, **19**:2958-2960.
47. Merkin J, Russell C, Chen P, Burge CB: **Evolutionary dynamics of gene and isoform regulation in mammalian tissues.** *Science* 2012, **338**:1593-1600.
48. Li Z, Bammann H, Li M, Liang H, Yan Z, Phoebe Chen Y-P, Zhao M, Khaitovich P: **Evolutionary and ontogenetic changes in RNA editing in human, chimpanzee, and macaque brains.** *RNA* 2013, **19**:1693-1702.
49. Shulha HP, Crisci JL, Reshetov D, Tushir JS, Cheung I, Bharadwaj R, Chou H-J, Houston IB, Peter CJ, Mitchell AC *et al.*: **Human-specific histone methylation signatures at transcription start sites in prefrontal neurons.** *PLoS Biol* 2012, **10**:e1001427.
50. Khaitovich P, Paabo S, Weiss G: **Toward a neutral evolutionary model of gene expression.** *Genetics* 2005, **170**:929-939.
51. Chaix R, Somel M, Kreil DP, Khaitovich P, Lunter GA: **Evolution of primate gene expression: drift and corrective sweeps?** *Genetics* 2008, **180**:1379-1389.
52. Khan Z, Ford MJ, Cusanovich DA, Mitrano A, Pritchard JK, Gilad Y: **Primate transcript and protein expression levels evolve under compensatory selection pressures.** *Science* 2013, **342**:1100-1104.
- This study compared transcriptome and proteome differences between human and chimpanzee cell lines using RNA-sequencing and mass spectrometry, respectively, and found that the proteome is significantly more conserved, especially for genes conserved at the sequence level.
53. Fraser HB, Moses AM, Schadt EE: **Evidence for widespread adaptive evolution of gene expression in budding yeast.** *Proc Natl Acad Sci U S A* 2010, **107**:2977-2982.
54. Fraser HB, Levy S, Chavan A, Shah HB, Perez JC, Zhou Y, Siegal ML, Sinha H: **Polygenic cis-regulatory adaptation in the evolution of yeast pathogenicity.** *Genome Res* 2012, **22**:1930-1939.
55. Perry GH, Melsted P, Marioni JC, Wang Y, Bainer R, Pickrell JK, Michelini K, Zehr S, Yoder AD, Stephens M *et al.*: **Comparative RNA sequencing reveals substantial genetic variation in endangered primates.** *Genome Res* 2012, **22**:602-610.
56. Konopka G, Geschwind DH: **Human brain evolution: harnessing the genomics (r)evolution to link genes, cognition, and behavior.** *Neuron* 2010, **68**:231-244.
57. Somel M, Franz H, Yan Z, Lorenc A, Guo S, Giger T, Kelso J, Nickel B, Dannemann M, Bahn S *et al.*: **Transcriptional neoteny in the human brain.** *Proc Natl Acad Sci U S A* 2009, **106**:5743-5748.
58. Somel M, Guo S, Fu N, Yan Z, Hu HY, Xu Y, Yuan Y, Ning Z, Hu Y, Menzel C *et al.*: **Microrna, mRNA, and protein expression link development and aging in human and macaque brain.** *Genome Res* 2010, **20**:1207-1218.
59. Fraser H, Khaitovich P, Plotkin J, bo S, Eisen M: **Aging and gene expression in the primate brain.** *PLoS Biol* 2005:3.
60. Smith BH, Crummett TL, Brandt KL: **Ages of eruption of primate teeth: a compendium for aging individuals and comparing life histories.** *Am J Phys Anthropol* 1994, **37**:177-231.
61. Walker R, Hill K, Burger O, Hurtado AM: **Life in the slow lane revisited: ontogenetic separation between chimpanzees and humans.** *Am J Phys Anthropol* 2006, **129**:577-583.
62. Gould S: *Ontogeny and Phylogeny*. Harvard University Press; 1977.
63. Shea B: **Heterochrony in human evolution: the case for neoteny reconsidered.** *Am J Phys Anthropol* 1989, **32**:69-101.
- A comprehensive review of comparative ontogenetic analysis methods. Shea suggests here that general human features are too divergent from chimpanzees so as to be directly explained by neoteny, whereas bonobo features can be readily explained by neoteny.
64. Liu X, Somel M, Tang L, Yan Z, Jiang X, Guo S, Yuan Y, He L, Oleksiak A, Zhang Y *et al.*: **Extension of cortical synaptic development distinguishes humans from chimpanzees and macaques.** *Genome Res* 2012, **22**:611-622.
- This comparison of postnatal primate brain development in PFC and cerebellum finds a signal for an extension of synaptic development specifically in the human PFC, and studies the regulation of this change.
65. McLean CY, Reno PL, Pollen AA, Bassan AI, Capellini TD, Guenther C, Indjeian VB, Lim X, Menke DB, Schaar BT *et al.*: **Human-specific loss of regulatory DNA and the evolution of human-specific traits.** *Nature* 2011, **471**:216-219.
66. Charrier C, Joshi K, Coutinho-Budd J, Kim J-E, Lambert N, de Marchena J, Jin W-L, Vanderhaeghen P, Ghosh A, Sassa T *et al.*: **Inhibition of srgap2 function by its human-specific paralogs induces neoteny during spine maturation.** *Cell* 2012, **149**:923-935.
- An elegant example of how a partial gene duplication in human evolution could have altered neuronal morphogenesis and boosted dendritic spine density.
67. Prabhakar S, Noonan J, Paabo S, Rubin E: **Accelerated evolution of conserved noncoding sequences in humans.** *Science* 2006, **314**:786-790.
68. Pollard K, Salama S, King B, Kern A, Dreszer T, Katzman S, Siepel A, Pedersen J, Bejerano G, Baertsch R *et al.*: **Forces shaping the fastest evolving regions in the human genome.** *PLoS Genet* 2006, **2**:e168.
69. Nowick K, Hamilton AT, Zhang H, Stubbs L: **Rapid sequence and expression divergence suggest selection for novel function in primate-specific KRAB-ZNF genes.** *Mol Biol Evol* 2010, **27**:2606-2610.
70. Zhang YE, Landback P, Vibranovski MD, Long M: **Accelerated recruitment of new brain development genes into the human genome.** *PLoS Biol* 2011, **9**:e1001179.

71. Hu HY, He L, Fominykh K, Yan Z, Guo S, Zhang X, Taylor MS, Tang L, Li J, Liu J *et al.*: **Evolution of the human-specific microRNA miR-941**. *Nat Commun* 2012, **3**:1145.
72. Haygood R, Fedrigo O, Hanson B, Yokoyama K-D, Wray GA: **Promoter regions of many neural- and nutrition-related genes have experienced positive selection during human evolution**. *Nat Genet* 2007, **39**:1140-1144.
73. Giger T, Khaitovich P, Somel M, Lorenc A, Lizano E, Harris L, Ryan M, Lan M, Wayland M, Bahn S *et al.*: **Evolution of neuronal and endothelial transcriptomes in primates**. *Genome Biol Evol* 2010, **evq018**:v011.
74. Pollard K, Salama S, Lambert N, Lambot M-A, Coppens S, Pedersen J, Katzman S, King B, Onodera C, Siepel A *et al.*: **An RNA gene expressed during cortical development evolved rapidly in humans**. *Nature* 2006, **443**:167-172.
75. Prabhakar S, Visel A, Akiyama J, Shoukry M, Lewis K, Holt A, Plajzer-Frick I, Morrison H, FitzPatrick D, Afzal V *et al.*: **Human-specific gain of function in a developmental enhancer**. *Science* 2008, **321**:1346-1350.
76. Zeder MA: **Pathways to animal domestication**. In *Biodiversity in Agriculture: Domestication, Evolution, and Sustainability*. Edited by Gepts P, Famula TR, Bettinger RL. Cambridge University Press; 2012.
77. Seid M, Wehner R: **Delayed axonal pruning in the ant brain: a study of developmental trajectories**. *Dev Neurobiol* 2009, **69**:350-364.
78. Hsieh W-P, Chu T-M, Wolfinger R, Gibson G: **Mixed-model reanalysis of primate data suggests tissue and species biases in oligonucleotide-based gene expression profiles**. *Genetics* 2003, **165**:747-757.
79. Nuzhdin SV, Wayne ML, Harmon KL, McIntyre LM: **Common pattern of evolution of gene expression level and protein sequence in Drosophila**. *Mol Biol Evol* 2004, **21**:1308-1317.
80. Yanai I, Graur D, Ophir R: **Incongruent expression profiles between human and mouse orthologous genes suggest widespread neutral evolution of transcription control**. *OMICS: J Integr Biol* 2004, **8**:15-24.
81. Lemos B, Meiklejohn C, Caceres M, Hartl D: **Rates of divergence in gene expression profiles of primates, mice, and flies: stabilizing selection and variability among functional categories**. *Evolution* 2005, **59**:126-137.
82. Khaitovich P, Kelso J, Franz H, Visagie J, Giger T, Joerchel S, Petzold E, Green R, Lachmann M, bo S: **Functionality of intergenic transcription: an evolutionary comparison**. *PLoS Genet* 2006, **2**:e171.
83. Whitehead A, Crawford D: **Variation within and among species in gene expression: raw material for evolution**. *Mol Ecol* 2006, **15**:1197-1211.
84. Felsenstein J: **Phylogenies and the comparative method**. *Am Nat* 1985:1-15.
85. Hansen TF: **Stabilizing selection and the comparative analysis of adaptation**. *Evolution* 1997, **51**:1341-1351.
86. Butler MA, King AA: **Phylogenetic comparative analysis: a modeling approach for adaptive evolution**. *Am Nat* 2004, **164**:683-695.
87. Hansen TF, Pienaar J, Orzack SH: **A comparative method for studying adaptation to a randomly evolving environment**. *Evolution* 2008, **62**:1965-1977.
88. O'Meara BC, Beaulieu JM: **Modelling stabilizing selection: the attraction of Ornstein-Uhlenbeck models**. In *Modern Phylogenetic Comparative Methods and Their Application in Evolutionary Biology*. Edited by Garamszegi LZ. Springer-Verlag; 2014.
89. Rohlf RV, Harrigan P, Nielsen R: **Modeling gene expression evolution with an extended Ornstein-Uhlenbeck process accounting for within-species variation**. *Mol Biol Evol* 2014, **31**:201-211.
90. Kalinka AT, Varga KM, Gerrard DT, Preibisch S, Corcoran DL, Jarrells J, Ohler U, Bergman CM, Tomancak P: **Gene expression divergence recapitulates the developmental hourglass model**. *Nature* 2010, **468**:811-814.
91. Rohlf RV, Nielsen R: **Identifying adaptive and plastic gene expression levels using a unified model for expression variance between and within species**. *bioRxiv* 2014.
92. Gruber JD, Vogel K, Kalay G, Wittkopp PJ: **Contrasting properties of gene-specific regulatory, coding, and copy number mutations in saccharomyces cerevisiae: frequency, effects, and dominance**. *PLoS Genet* 2012, **8**:e1002497.
93. Huttenlocher PR, Dabholkar AS: **Regional differences in synaptogenesis in human cerebral cortex**. *J Comp Neurol* 1997, **387**:167-178.
94. Huttenlocher PR, de Courten C, Garey LJ, Van der Loos H: **Synaptogenesis in human visual cortex – evidence for synapse elimination during normal development**. *Neurosci Lett* 1982, **33**:247-252.
95. Bianchi S, Stimpson CD, Duka T, Larsen MD, Janssen WGM, Collins Z, Bauernfeind AL, Schapiro SJ, Baze WB, McArthur MJ *et al.*: **Synaptogenesis and development of pyramidal neuron dendritic morphology in the chimpanzee neocortex resembles humans**. *Proc Natl Acad Sci U S A* 2013, **110**(Suppl2):10395-10401.
96. Goyal MS, Hawrylycz M, Miller JA, Snyder AZ, Raichle ME: **Aerobic glycolysis in the human brain is associated with development and neoteny gene expression**. *Cell Metab* 2014, **19**:49-57.
97. Bogin B: **Evolutionary hypotheses for human childhood**. *Yearb Phys Anthropol* 1997, **40**:63-89.
98. Johnson M: **Functional brain development in humans**. *Nat Rev Neurosci* 2001, **2**:475-483.
99. de Graaf-Peters VB, Hadders-Algra M: **Ontogeny of the human central nervous system: what is happening when?** *Early Hum Dev* 2006, **82**:257-266.
100. Buřill E, Agustí J, Blesa R: **Human neoteny revisited: the case of synaptic plasticity**. *Am J Hum Biol* 2011, **23**:729-739.
101. Shalizi A, Gaudillière B, Yuan Z, Stegmüller J, Shirogane T, Ge Q, Tan Y, Schulman B, Harper JW, Bonni A: **A calcium-regulated mef2 sumoylation switch controls postsynaptic differentiation**. *Science* 2006, **311**:1012-1017.
102. Flavell SW, Cowan CW, Kim T-K, Greer PL, Lin Y, Paradis S, Griffith EC, Hu LS, Chen C, Greenberg ME: **Activity-dependent regulation of mef2 transcription factors suppresses excitatory synapse number**. *Science* 2006, **311**:1008-1012.
103. Somel M, Liu X, Khaitovich P: **Human brain evolution: transcripts, metabolites and their regulators**. *Nat Rev Neurosci* 2013, **14**:112-127.
104. Fisher SE, Ridley M: **Evolution, culture, genes, and the human revolution**. *Science* 2013, **340**:929-930.
105. Herculano-Houzel S: **The remarkable, yet not extraordinary, human brain as a scaled-up primate brain and its associated cost**. *Proc Natl Acad Sci U S A* 2012, **109**(Suppl1):10661-10668.
106. Rilling JK, Insel TR: **The primate neocortex in comparative perspective using magnetic resonance imaging**. *J Hum Evol* 1999, **37**:191-223.
107. Rilling JK, Seligman RA: **A quantitative morphometric comparative analysis of the primate temporal lobe**. *J Hum Evol* 2002, **42**:505-533.
108. Schenker NM, Hopkins WD, Spocter MA, Garrison AR, Stimpson CD, Erwin JM, Hof PR, Sherwood CC: **Broca's area homologue in chimpanzees (pan troglodytes): probabilistic mapping, asymmetry, and comparison to humans**. *Cereb Cortex* 2010, **20**:730-742.
109. Rilling JK, Glasser MF, Preuss TM, Ma X, Zhao T, Hu X, Behrens TEJ: **The evolution of the arcuate fasciculus revealed with comparative dti**. *Nat Neurosci* 2008, **11**:426-428.

110. Li L, Hu X, Preuss TM, Glasser MF, Damen FW, Qiu Y, Rilling J: **Mapping putative hubs in human, chimpanzee and rhesus macaque connectomes via diffusion tractography.** *Neuroimage* 2013, **80**:462-474.
111. Nimchinsky EA, Gilissen E, Allman JM, Perl DP, Erwin JM, Hof PR: **A neuronal morphologic type unique to humans and great apes.** *Proc Natl Acad Sci U S A* 1999, **96**:5268-5273.
112. Semendeferi K, Teffer K, Buxhoeveden DP, Park MS, Bludau S, Amunts K, Travis K, Buckwalter J: **Spatial organization of neurons in the frontal pole sets humans apart from great apes.** *Cereb Cortex* 2010, **21**:1485-1497.
113. Spocter MA, Hopkins WD, Barks SK, Bianchi S, Hehmeyer AE, Anderson SM, Stimpson CD, Fobbs AJ, Hof PR, Sherwood CC: **Neuropil distribution in the cerebral cortex differs between humans and chimpanzees.** *J Comp Neurol* 2012, **520**:2917-2929.
114. Teffer K, Buxhoeveden DP, Stimpson CD, Fobbs AJ, Schapiro SJ, Baze WB, McArthur MJ, Hopkins WD, Hof PR, Sherwood CC *et al.*: **Developmental changes in the spatial organization of neurons in the neocortex of humans and common chimpanzees.** *J Comp Neurol* 2013, **521**:4249-4259.
115. Schenker NM, Buxhoeveden DP, Blackmon WL, Amunts K, Zilles K, Semendeferi K: **A comparative quantitative analysis of cytoarchitecture and minicolumnar organization in broca's area in humans and great apes.** *J Comp Neurol* 2008, **510**:117-128.
116. Buxhoeveden DP, Switala AE, Litaker M, Roy E, Casanova MF: **Lateralization of minicolumns in human planum temporale is absent in nonhuman primate cortex.** *Brain Behav Evol* 2001, **57**:349-358.
117. Bianchi S, Stimpson CD, Bauernfeind AL, Schapiro SJ, Baze WB, McArthur MJ, Bronson E, Hopkins WD, Semendeferi K, Jacobs B *et al.*: **Dendritic morphology of pyramidal neurons in the chimpanzee neocortex: regional specializations and comparison to humans.** *Cereb Cortex* 2013, **23**:2429-2436.
118. Allman JM, Tetreault NA, Hakeem AY, Manaye KF, Semendeferi K, Erwin JM, Park S, Goubert V, Hof PR: **The von economo neurons in the fronto-insular and anterior cingulate cortex.** *Ann NY Acad Sci* 2011, **1225**:59-71.
119. Sakai T, Hirata S, Fuwa K, Sugama K, Kusunoki K, Makishima H, Eguchi T, Yamada S, Ogihara N, Takeshita H: **Fetal brain development in chimpanzees versus humans.** *Curr Biol* 2012, **22**:R791-R792.
120. Leigh SR: **Brain growth, life history, and cognition in primate and human evolution.** *Am J Primatol* 2004, **62**:139-164.
121. Sakai T, Mikami A, Tomonaga M, Matsui M, Suzuki J, Hamada Y, Tanaka M, Miyabe-Nishiwaki T, Makishima H, Nakatsukasa M *et al.*: **Differential prefrontal white matter development in chimpanzees and humans.** *Curr Biol* 2011, **21**:1397-1402.
122. Chen X, Errangi B, Li L, Glasser MF, Westlye LT, Fjell AM, Walhovd KB, Hu X, Herndon JG, Preuss TM *et al.*: **Brain aging in humans, chimpanzees (*Pan troglodytes*), and rhesus macaques (*Macaca mulatta*): magnetic resonance imaging studies of macro- and microstructural changes.** *Neurobiol Aging* 2013, **34**:2248-2260.
123. Sherwood CC, Gordon AD, Allen JS, Phillips KA, Erwin JM, Hof PR, Hopkins WD: **Aging of the cerebral cortex differs between humans and chimpanzees.** *Proc Natl Acad Sci U S A* 2011, **108**:13029-13034.
124. Rilling JK, Barks SK, Parr LA, Preuss TM, Faber TL, Pagnoni G, Bremner JD, Votaw JR: **A comparison of resting-state brain activity in humans and chimpanzees.** *Proc Natl Acad Sci U S A* 2007, **104**:17146-17151.
125. Duka T, Anderson SM, Collins Z, Raghanti MA, Ely JJ, Hof PR, Wildman DE, Goodman M, Grossman LI, Sherwood CC: **Synaptosomal lactate dehydrogenase isoenzyme composition is shifted toward aerobic forms in primate brain evolution.** *Brain Behav Evol* 2014, **83**:216-230.
126. Fedrigo O, Pfefferle AD, Babbitt CC, Haygood R, Wall CE, Wray GA: **A potential role for glucose transporters in the evolution of human brain size.** *Brain Behav Evol* 2011, **78**:315-326.